The Invention

The invention is directed to compositions and methods for internally labeling a cell. The composition of claim 1 comprises (1) a ligand which specifically binds to a cell surface antigen and becomes internalized by the cell, (2) an oligopeptide which comprises at least one positively-charged amino acid residue and at least one D-amino acid residue and is covalently bound to the ligand; and (3) a label which is covalently bound to the oligopeptide. Dependent claims 2-21 and 44-47 specify the features of the ligand, the oligopeptide, and the label in various embodiments.

The Rejection of Claims 1-8, 11-21, and 44-47 Under 35 U.S.C. § 112, First Paragraph

Claims 1-8, 11-21, and 44-47 stand rejected under 35 U.S.C. 112, first paragraph. The Office Action states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor had possession of the claimed invention at the time the application was filed. The Applicant respectfully traverses this rejection.

The Office Action asserts that the specification sets forth only antibodies and antibody fragments which bind to EGFRvIII. The Office Action further states that no disclosure is made of ligands which bind to other internalizing receptors beyond mere contemplation, and this is insufficient to support the instant claims to a composition comprising a ligand which specifically binds to a "surface antigen of a cell." Office Action, page 2, line 15 to page 3, line 2. Applicant respectfully urges that the claimed subject matter was described in the specification in such a way as to reasonably convey to one of skill in the art that the inventor had possession of the claimed invention at the time the application was filed.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, & 1, "Written Description" Requirement state that "[i]nformation which is well known in the art need not be described in detail in the specification" (66 Fed. Reg. 1099, at 1105, col. 3, lines 39-41 (Jan. 5, 2001)); "[t]he description need only describe in detail that which is new or not conventional" (*Id.* at 1105, col. 1, lines 17-19); and "[w]hat is conventional or well known to one of ordinary skill in the art need not be disclosed in detail" (*Id.* at 1106, col. 1, lines 34-36).

Applicant submits that the existence of many internalizing cell surface antigens and ligands that bind specifically to them was well known in the art. Examples of internalizing cell surface receptors which were known at the time of the invention include: G protein coupled receptors (Segredo et al., J. Neurochem. 68: 2395-404(1997)), collagen receptor (Lee et al., J. Cell Physiol. 168: 695-704 (1996)), beta-2 adrenegic receptor (Morrison et al., Mol. Pharmacol. 50:692-9 (1996)), low density lipoprotein receptor-related protein (receptor of chylomicron remnants and protease-inhibitor complexes)(Warshawsky et al., Eur. J. Cell Biol. 69:156-65 (1996)), GPI-linked membrane folate receptors (Rijnboutt et al., J. Cell Biol. 132:35-47 (1996), alpha-2 macroglobulin receptor (Grofova et al., Neoplasma 42:97-103 (1995), TrkA and p75 receptor (Saragovi et al., 273:34933-40 (1998)), and IgG receptor (CD32)(Van Den Herik-Oudijk et al., J. Immunol. 152:574-85 (1994). Numerous publications have taught this phenomenon. Thus, there is no need for such well-known information to be described in detail in the Applicant's specification. The specific binding between cell surface antigens and their ligands is so well characterized that a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every possible example is not explicitly listed in the specification.

Moreover, the specification specifically cites references which disclose numerous examples of such ligand-cell surface antigen binding pairs. Mattes *et. al.* (cited at page 11, lines 22-23 of the instant specification) discloses 12 different antibodies that specifically bind as ligands to 10 different cell surface antigens, some of which are well known receptors. In addition, numerous other publications were cited in the specification which disclose antibodies that specifically bind to a broad range of cell surface antigens and are internalized (see the chart below). Thus the rejection clearly errs when it asserts that only EGFRvIII and its ligands are disclosed.

Reference	**Citation in Specification**	**Ligand**	**Receptor/Surface-Antigen**
De Santes K, et al. Cancer Res 1992 Apr 1; 52(7): 1916-23	Page 11, line 20.	Radioiodinated murine monoclonal antibodies (muMABs) 4D5 and 7C2 (recognizing distinct epitopes on extracellular domain)	HER-2/neu oncogene (transmembrane phosphoglycoprotein)
Hansen HJ, et al. Biochem J 1996 Nov 15; 320 (Pt 1): 293-300	Page 11, line 23.	Antibody LL1, which reacts with the invariant chain (Ii) subunit of the immature MHC class-II antigen (CD74) on the surface of B-cell lymphomas	MHC class-II antigen (CD74)

Mattes MJ, et al. Cancer 1994 Feb 1; 73(3 Suppl): 787-93	Page 11, line 13.	12 antibodies: MA103 W6/32 MA48 MH99, MJ37, and RS11 MW207 SE9 RS7 NP4 YTH53.1 9.2.27	10 cell surface antigens: Glycoprotein, 50-55kDa. Glycoprotein, HLA, ABC 44/12 kDa. Glycoprotein,140/14028 kDa VLA-3 or 3 chain. Glycoprotein 38/29 kDa. Protein, 37 kDa folic acid receptor. Glycoprotein 95/95 kDa transferrin receptor. Glycoprotein 46 kDa. CEA. CD59. Melanoma proteoglycan.
Novak-Hofer I, et al. Int J Cancer 1994 May 1; 57(3): 427-32	Page 17, line 29.	Chimeric monoclonal anti-neuroblastoma antibody (MAb chCE7)	Neuroblastoma-associated cell-surface glycoprotein 190 kDa
Press OW, et al. Lancet 1995 Aug 5; 346(8971): 336-40	Page 17, line 29.	Anti-CD20 (B1) antibody	CD20 (B1) from B-cell Lymphoma
Sharkey RM, et al. Cancer Immunol Immunother 1997 May; 44(3): 179-88	Page 11, line 24.	LL2 (anti-CD22 pan-B-cell monoclonal antibody) or its fragments (F(ab')2, Fab')	CD-22 for B-cell of non-Hodgkin's lymphoma (NHL)
Stein R, et al. 1: Cancer Res 1995 Jul 15; 55(14): 3132-9	Page 17, line 20.	mAbs RS7 and RS11	Pancarcinoma integral membrane glycoproteins
Stein R, et al. J Nucl Med 1997 Mar; 38(3): 391-5	Page 17, line 21.	Labeled Mabs: RS7 RS11	Cell surface glycoprotein: EGP 1 EGP 2
van der Jagt RH, et al. Cancer Res 1992 Jan 1; 52(1): 89-94	Page 14, line 30.	Anti-CD33 antibody	CD33
Xu FJ, et al. Nucl Med Biol 1997 Jul; 24(5): 451-9	Page 11, line 20.	Seven monoclonal antibodies reactive with oncoprotein	HER-2/neu oncogene encodes a 185 kDa phosphoglycoprotein

The specification also discloses several ligands for the EGFRvIII cell surface antigen. These include chimeric human/mouse L8A4 (page 13, lines 20-29); monoclonal antibody Y10 (page 6, line 6); and monoclonal antibody H10 (page 6, line 6). Thus the specification taken as a whole describes a large family of ligands and cell surface receptors.

The Written Description Guidelines specify that the requirement for adequate description of a genus can be satisfied in one of several possible ways.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus....

66 Fed. Reg. 1099, at 1106 col. 3, lines 13-28 (Jan. 5, 2001).

- **Actual Reduction to Practice:** Applicant has demonstrated actual reduction to practice of monoclonal antibody L8A4 labeled with radioiodine via an oligopeptide. The labeled antibody specifically binds to EGFRvIII receptor and is internalized by cells (Examples 8 and 9, pages 28-30 of the instant specification).

- **Reduction to Drawings:** Figures 1A and 1B illustrate the scheme by which a monoclonal antibody is labeled via an oligopeptide linker. The monoclonal antibody is indicated generically because its particular structure is unimportant for the invention.

- **Disclosure of Relevant, Identifying Characteristics:** The application discloses that "any molecule which specifically binds to a cell surface antigen" can be used as a ligand (specification at page 5, lines 12-13, emphasis added). "A ligand is considered to bind specifically when it binds with an affinity constant of 10^6 M^{-1} or more, preferably 10^8 M^{-1} or

more." Page 5, lines 17-18. Such disclosure provides the chemical and functional characteristics of the surface antigen and the ligand.

Thus, the specification complies with the Guidelines for describing a genus. Withdrawal of this rejection is respectfully

For the reasons discussed above, the withdrawal of this rejection is respectfully requested.

Allowance of all pending claims is respectfully requested.

Respectfully submitted,

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